MODULATORS OF PERIPHERAL 5-HT RECEPTORS

FIELD OF THE INVENTION

The invention relates to modulators of peripheral 5-HT receptors, particularly 5-HT4, receptors said modulators essentially selective for peripheral 5-HT receptors over receptors of the central nervous system. The invention allows for the treatment, amongst others, of gastrointestinal disorders, lower urinary tract disorders, and cardiovascular disorders without side effects related to CNS activity.

BACKGROUND OF THE INVENTION

5-Hydroxytryptamine (5-HT) is an important signalling molecule in the human body, and has important effects both as a neurotransmitter and as a locally acting signalling molecule with e.g. vasoactive effects. During the past 20 years 14 different 5-HT receptors have been identified and classified into 7 different subgroups (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7), based on structural and pharmacological criteria as well as signal transduction properties. Additional diversity arises from e.g. alternative splicing of e.g. 5-HT_4 (e.g. $5\text{-HT}_{4(a)}$, $5\text{-HT}_{4(b)}$ etc.) and 5-HT_7 receptors, and of RNA editing of e.g. 5-HT_{2C} receptors. 5-HT_4 is found to play a central role in diseases in organs like the heart, the gastrointestinal system, the urinary bladder and central nervous system (CNS).

5-HT_4 receptor modulators, agonists and antagonists alike, are found to be useful for the treatment of a variety of diseases such as gastroesophageal reflux disease, gastrointestinal disease, gastric motility disorder, non-ulcer dyspepsia, functional dyspepsia, irritable bowel syndrome, constipation, dyspepsia, oesophagitis, gastroesophageal disease, nausea, central nervous system disease, Alzheimer's disease, cognitive disorder, emesis, migraine, neurological disease, pain, and cardiovascular disorders such as cardiac failure and heart arrhythmia. Further gastrointestinal disorders suitable for prophylaxis or treatment of the symptoms of Irritable Bowel Syndrome, including abdominal pain and disrupted colonic motility.

Since 5-HT_4 receptors are located both inside and outside the CNS, 5-HT_4 receptor agonists and antagonists will have effects both inside and outside the CNS, unless their design prevents their access to or causes them to preferentially localise to only one of these compartments. When addressing 5-HT_4 receptors located outside the CNS, effects on receptors inside the CNS may represent undesirable side-effects of the treatment, and vice versa. The present invention seeks to avoid this problem by presenting 5-HT_4 receptor